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10/590,707	08/25/2006	Michitaka Sato	2006_1414A	3825

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WENDEROTH, LIND & PONACK, L.L.P.  
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WASHINGTON, DC 20006-1021

EXAMINER
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LEESER, ERICH A

ART UNIT	PAPER NUMBER
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1624

MAIL DATE	DELIVERY MODE
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10/02/2007

PAPER

**Please find below and/or attached an Office communication concerning this application or proceeding.**

The time period for reply, if any, is set in the attached communication.

## Office Action Summary

Application No.

10/590,707

Applicant(s)

SATO ET AL.

Examiner

Erich A. Leeser

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1624

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

### Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

### Status

- 1) ☐ Responsive to communication(s) filed on \_\_\_\_.
- 2a) ☐ This action is FINAL. 2b) ☒ This action is non-final.
- 3) ☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

### Disposition of Claims

- 4) ☒ Claim(s) 1-25 is/are pending in the application.
- 4a) Of the above claim(s) \_\_\_\_ is/are withdrawn from consideration.
- 5) ☐ Claim(s) \_\_\_\_ is/are allowed.
- 6) ☒ Claim(s) 1-25 is/are rejected.
- 7) ☐ Claim(s) \_\_\_\_ is/are objected to.
- 8) ☐ Claim(s) \_\_\_\_ are subject to restriction and/or election requirement.

### Application Papers

- 9) ☐ The specification is objected to by the Examiner.
- 10) ☐ The drawing(s) filed on \_\_\_\_ is/are: a) ☐ accepted or b) ☐ objected to by the Examiner.  
Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).  
Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).
- 11) ☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

### Priority under 35 U.S.C. § 119

- 12) ☒ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).
- a) ☒ All b) ☐ Some \* c) ☐ None of:
- ☒ Certified copies of the priority documents have been received.
  - ☐ Certified copies of the priority documents have been received in Application No. \_\_\_\_.
  - ☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).
- \* See the attached detailed Office action for a list of the certified copies not received.

### Attachment(s)

- 1) ☒ Notice of References Cited (PTO-892)
- 2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
- 3) ☒ Information Disclosure Statement(s) (PTO/SB/08)  
Paper No(s)/Mail Date November 14, 2006.

- 4) ☐ Interview Summary (PTO-413)  
Paper No(s)/Mail Date. \_\_\_\_.
- 5) ☐ Notice of Informal Patent Application
- 6) ☐ Other: \_\_\_\_.

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### **DETAILED ACTION**

Claims 1-25 are currently pending and under examination.

#### ***Priority***

Acknowledgement is made that this application is a 371 of PCT/JP05/03691, filed on February 25, 2005, and which claims benefit of foreign applications JAPAN 2004-52040, filed on February 26, 2004 and JAPAN 2004-322858, filed on November 5, 2004.

#### ***Information Disclosure Statement***

The references in the IDS dated November 14, 2006, are made of record.

#### ***Claim Rejections 35 U.S.C. § 112***

The following is a quotation of the second paragraph of 35 U.S.C. 112:

The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

Claim 1 and 17 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which Applicant regards as the invention. The following apply.

(a) Specifically, claim 1 is rejected because the claim language is unclear as to the number or range of atoms included in the “remainder of the group” of variable group B.

Correction is required.

(b) Claim 17 is rejected because “therapeutic method of irritable [bowel] syndrome” is unclear because as written, it implies that it is a method to induce IBS instead of treating it. It appears that this claim was literally translated from the original Japanese, resulting in a non-sensical claim. Cancellation is recommended.

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The following is a quotation of the first paragraph of 35 U.S.C. 112:

The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 16-22 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the enablement requirement because the specification does not enable the instant compounds to treat irritable bowel syndrome, depression and the other diseases and conditions listed in claim 16 comprising administering a therapeutically-effective amount of a compound of formula (I) or enable one skilled in the art to which it pertains, or with which it is most nearly connected, to use the invention.

There are many factors to be considered when determining whether there is sufficient evidence to support a determination that a disclosure does not satisfy the enablement requirement and whether any necessary experimentation is “undue.” These factors include 1) the breadth of the claims, 2) the nature of the invention, 3) the state of the prior art, 4) the level of one of ordinary skill, 5) the level of predictability in the art, 6) the amount of direction provided by the inventor, 7) the existence of working examples, and 8) the quantity of experimentation needed to make or use the invention based on the content of the disclosure. *In re Wands*, 858 F.2d 731, 737, 8 USPQ2d 1400, 1404 (Fed. Cir. 1988).

**The nature of the invention:**

The instant invention is drawn to compositions used to treat irritable bowel syndrome, depression and the other diseases and conditions listed in claim 16 comprising administering a therapeutically-effective amount of a compound of formula (I).

**The state of the prior art:**

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The state of the prior art involves screening *in vitro* and *in vivo* to determine which compounds exhibit the desired pharmacological activities (i.e. what compounds can treat which specific disease). There is no absolute predictability even in view of the seeming high level of skill in the art. The existence of these obstacles establishes that the contemporary knowledge in the art would prevent one of ordinary skill in the art from accepting any therapeutic regimen on its face. For example, “the key for the next generation of progress is to unravel the complex effects of activation/antagonism of the various postsynaptic 5-HT receptors and their significance, *if any*, in mediating the antidepressant response.” (Emphasis added). Cryan, J., et al., *5-HT<sub>1A</sub> and Beyond: The Role of Serotonin and its Receptors in Depression and the Antidepressant Response*, Hum. Psychopharmacol. Clin. Exp. 15, 113-135 (2000). This reference shows the speculative nature of the role of 5-HT receptors with the treatment of depression.

**The predictability in the art:**

It is noted that the pharmaceutical art is unpredictable, requiring each embodiment to be individually assessed for physiological activity. *In re Fisher*, 427 F. 2d 833, 166 USPQ 18 (CCPA 1970) indicates that the more unpredictable an area is, the more specific enablement is necessary in order to satisfy the statute. In the instant case, the claimed invention is highly unpredictable since one skilled in the art would not necessarily recognize, with regards to therapeutic effects, whether or not the compounds of formula (I) would be useful to irritable bowel syndrome, depression and the other diseases and conditions listed in claim 16.

**Amount of guidance/working examples:**

Although Applicant includes five assays on pages 45-58 of the specification, neither of these definitively show that the instant compounds can reliably be used to treat irritable bowel syndrome, depression and the other diseases and conditions listed in claim 16 comprising administering a therapeutically-effective amount of a compound of formula (I).

**The breadth of the claims:**

The claim terms are not unduly broad.

**The quantity of undue experimentation needed:**

Since the guidance and teaching provided by the specification is insufficient to treat irritable bowel syndrome, depression and the other diseases and conditions listed in claim 16 comprising administering a therapeutically-effective amount of a compound of formula (I), one of ordinary skill in the art, even with a high level of skill, is unable to practice the invention as claimed without undue experimentation.

**The level of the skill in the art:**

The level of skill in the art is high. Due to the unpredictability in the pharmaceutical art; however, it is noted that each embodiment of the invention is required to be individually assessed for physiological activity by *in vitro* and *in vivo* screening to determine which compounds exhibit the desired pharmacological activity and which diseases or diseases would benefit from this activity.

Taking all of the above factors into consideration, it is not seen how one of ordinary skill in the art would be able to use Applicant's invention to treat irritable bowel syndrome, depression and the other diseases and conditions listed in claim 16 comprising administering a therapeutically-effective amount of a compound of formula (I) without undue experimentation.

***Claim Rejections 35 U.S.C. § 103***

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

(a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negated by the manner in which the invention was made.

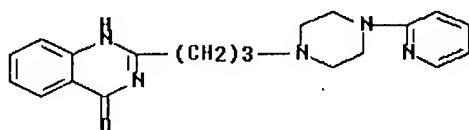
The factual inquiries set forth in *Graham v. John Deere Co.*, 383 U.S. 1, 148 USPQ 459 (1966), that are applied for establishing a background for determining obviousness under 35 U.S.C. 103(a) are summarized as follows:

1. Determining the scope and contents of the prior art.
2. Ascertaining the differences between the prior art and the claims at issue.
3. Resolving the level of ordinary skill in the pertinent art.
4. Considering objective evidence present in the application indicating obviousness or nonobviousness.

Claims 1-2, 7, 9-11, 13 and 15 are rejected under 35 U.S.C. § 103(a) as being unpatentable over Matsuoka, et al., Canada Patent No. 2431406.

Matsuoka, et al., teaches piperazine compounds useful in the treatment of NMDA- and NO-induced toxicity, tissue damage from apoptosis, etc. Generically, claim 1 of the reference renders the scope of instant claim 1 obvious. For example, the following compounds of the reference render instant claim 1 obvious:

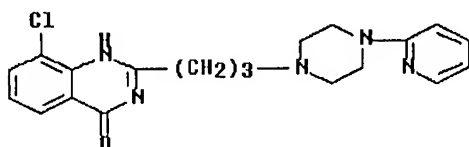
2-[3-[4-(2-pyridinyl)-1-piperazinyl]propyl]-4(1H)-Quinazolinone



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when Z is carbon, B is monocyclic,  $X^1$  and  $X^2$  are both hydrogen, Y is a direct bond, n is 2,  $R^1$  is hydrogen and A is i); and

8-chloro-2-[3-[4-(2-pyridinyl)-1-piperazinyl]propyl]-4(1H)-Quinazolinone



when Z is carbon, B is monocyclic,  $X^1$  and  $X^2$  are both hydrogen, Y is a direct bond, n is 2,  $R^1$  is halogen and A is i).

The instant claimed compounds would have been obvious, because one skilled in the art would have been motivated to prepare compounds as taught in the reference with the expectation of obtaining compounds falling within the generic teaching of claim 1. Therefore, the instant claimed compounds would have been suggested to one skilled in the art.

Thus, it would have been obvious to one having ordinary skill in the art at the time that the invention was made to make similar compounds of Matsuoka, et al.

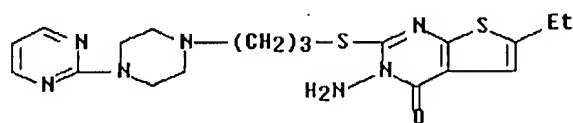
Claims 1, 6, 8-11, 13-15 and 23-25 are rejected under 35 U.S.C. § 103(a) as being unpatentable over Modica et al., *High Potent and Selective Arylpiperazine Derivatives as Ligands for the 5-HT<sub>1A</sub> Receptor*, Bioorganic & Medicinal Chemistry Letters, 10(10), 1089-1092 (2000).

Modica et al., teaches selective arylpiperazine derivatives as ligands for the 5-HT<sub>1A</sub> receptor very much like the compounds of the instant claims. Generically, claim 1 of the reference renders the scope of instant claim 1 obvious. For example, the following compounds of the reference render instant claim 1 obvious:



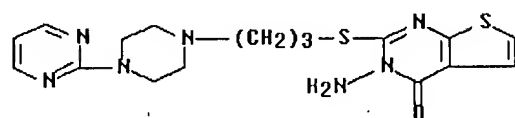
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3-amino-6-ethyl-2-[[3-[4-(2-pyrimidinyl)-1-piperazinyl]propyl]thio]-thieno[2,3-d]pyrimidin-4(3H)-one



when Z is nitrogen, B is monocyclic, X<sup>1</sup> is amino, X<sup>2</sup> is hydrogen, Y is sulfur, n is 2, R<sup>5</sup> is lower alkyl and A is v); and

3-amino-2-[[3-[4-(2-pyrimidinyl)-1-piperazinyl]propyl]thio]-thieno[2,3-d]pyrimidin-4(3H)-one



when Z is nitrogen, B is monocyclic, X<sup>1</sup> is amino, X<sup>2</sup> is hydrogen, Y is sulfur, n is 2, R<sup>5</sup> is hydrogen and A is v);

The instant claimed compounds would have been obvious, because one skilled in the art would have been motivated to prepare compounds as taught in the reference with the expectation of obtaining compounds falling within the generic teaching of claim 1. Therefore, the instant claimed compounds would have been suggested to one skilled in the art.

Thus, it would have been obvious to one having ordinary skill in the art at the time that the invention was made to make similar compounds of Modica, et al.

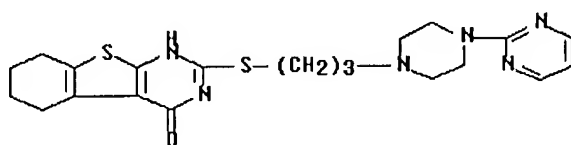
Claims 1, 6-7, 9-11, 13-16 and 23-25 are rejected under 35 U.S.C. § 103(a) as being unpatentable over Guccione, et al., *3D-QSAR Using "Multiconformer" Alignment: The Use of*

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*HASL in the Analysis of 5-HT1A Thienopyrimidinone Ligands*, Journal of Computer-Aided Molecular Design, 14(7), 647-657 (2000).

Guccione et al., teaches thienopyrimidinone ligands for the 5-HT1A receptor very much like the compounds of the instant claims. Generically, claim 1 of the reference renders the scope of instant claim 1 obvious. For example, the following compounds of the reference render instant claim 1 obvious:

5,6,7,8-tetrahydro-2-[[3-[4-(2-pyrimidinyl)-1-piperazinyl]propyl]thio]-[1]benzothieno[2,3-d]pyrimidin-4(1H)-one



when Z is nitrogen, B is monocyclic, X<sup>1</sup> and X<sup>2</sup> are both hydrogen, Y is sulfur, n is 2, R<sup>6</sup> is hydrogen and A is vi).

The instant claimed compounds would have been obvious, because one skilled in the art would have been motivated to prepare compounds as taught in the reference with the expectation of obtaining compounds falling within the generic teaching of claim 1. Therefore, the instant claimed compounds would have been suggested to one skilled in the art.

Thus, it would have been obvious to one having ordinary skill in the art at the time that the invention was made to make similar compounds of Guccione, et al.

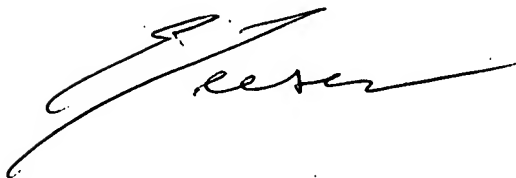
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***Conclusion***

Any inquiry concerning this communication or earlier communications from the Examiner should be directed to Erich A. Leeser whose telephone number is 571-272-9932. The Examiner can normally be reached Monday through Friday from 8:30 to 6:00 EST.

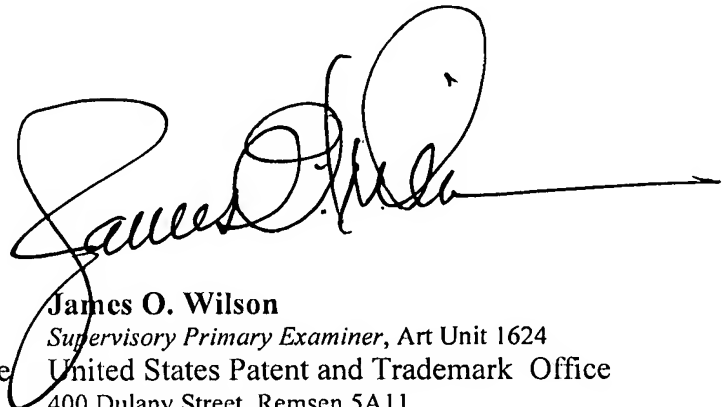
If attempts to reach the Examiner by telephone are unsuccessful, the Examiner's supervisor, Mr. James O. Wilson can be reached at 571-272-0661. The fax number for the organization where this application is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see <http://pair-direct.uspto.gov>. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) toll-free at 866-217-9197. If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.



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